Optimisation of tocilizumab therapy in giant cell arteritis. A multicentre real-life study of 471 patients

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Abstract

Objective

Tocilizumab (TCZ) is the only biologic therapy approved for giant cell arteritis (GCA). There is general agreement on the initial/maintenance dose, duration of TCZ therapy is not well established. In GiACTA trial, after one year on TCZ, most patients had GCA relapse after withdrawal. The aim of this study is to assess the effectiveness and safety of TCZ therapy optimisation in a large unselected series of patients with GCA in a clinical practice scenario.

Methods

We carried out a multicentre study on 471 GCA patients treated with TCZ. Once prolonged remission was achieved (n=231) and based on a decision between patient and physician, TCZ was optimised (n=125). We compared optimised (TCZ_{OPT}) and not optimised ($TCZ_{NON-OPT}$) groups. Prolonged remission defined as normalisation of clinical and laboratory data for 6 months. Optimisation was carried out by decreasing TCZ dose and/or increasing dosing interval.

Results

We evaluated 231 GCA patients on TCZ in prolonged remission. At TCZ onset, no differences in demographic, clinical, or laboratory data were observed. First TCZ optimisation was performed after a median follow-up of 12[6-17] months. Intravenous TCZ was optimised from 8 to 4 mg/kg/4weeks in 44% patients, while subcutaneous TCZ was optimised from 162 mg/w to 162 mg/every-other-week in 65% cases.

At the end of follow-up, prolonged remission (78.2% vs. 84.2%; p=0.29) and relapses (5.6% vs. 10.4%, p=0.177) were similar in TCZ_{OPT} vs $TCZ_{NON-OPT}$. Severe infections were more frequent in $TCZ_{NON-OPT}$ (12.9% vs. 6.6%; p=0.009).

Conclusion

TCZ optimisation may be done once complete remission is achieved by reducing dose or increasing dosing interval. This seems to be effective, safe and cost-effective therapeutic scheme.

Key words

giant cell arteritis, tocilizumab, optimisation, biological therapy

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Competing interests: page 835.

Introduction

Giant cell arteritis (GCA) is the most common type of vasculitis in European people over 50, and in North Americans of European ancestry, reaching a peak in patients of 70–80 years old (1, 2).

Glucocorticoids (GC) are the treatment of choice in GCA. However, a high frequency of side effects related to GC and relapses have been reported (3). In this regard, Proven *et al*. reported adverse events associated with GC in up to 86% of GCA patients. (3) In addition, relapses may occur during GC tapering (2-6), leading to the use of other therapeutic alternatives. In this line, tocilizumab (TCZ) was approved in 2017 for the treatment of GCA by the European Medication Agency (EMA) and the Food and Drug Administration (FDA) based on two randomised clinical trials (7, 8).

Biologic therapy (BT) represents an important advance in the control of immune-mediated diseases. Regrettably, BT can lead to significant side effects and high costs for health care systems. Therefore, when clinical remission is achieved, it is important to try to optimise the dose of BT and even discontinue it, when possible.

There is scarce information on TCZ optimisation in GCA. The GiACTA study showed that after one year of weekly TCZ, most patients, (n=81, 95%) reached sustained remission and TCZ was stopped (8). However, in the extension phase of this study only 25 out of 59 (42%) patients maintained their treatment-free remission for another 2 years (9, 10). Therefore, most patients had GCA relapse after abrupt TCZ withdrawal. The optimisation of TCZ therapy in patients with GCA may be a way to reduce relapses, as well as the risk of adverse events (AEs) and drug costs when remission is reached.

Taking all these considerations into account, the present study aimed to assess whether the optimisation of TCZ in GCA patients, after reaching prolonged remission, is an effective and safe therapeutic option in a real-world clinical practice setting.

Patients and methods

Patients and enrolment criteria

We conducted an observational, retrospective, open-label multicentre study on 471 patients diagnosed with GCA and treated with TCZ at the Rheumatology or Autoimmune Units of 57 Spanish referral centres. Before TCZ onset, all of them had received high-dose GC, and 257 (54.6%) conventional synthetic and/or other biologic immunosuppressive agents. To reduce selection bias, we included all the patients who had received at least one dose of TCZ, regardless of the outcome. The design and main characteristics of the study have been previously described (11).

Briefly, the diagnosis of GCA was based on the American College of Rheumatology (ACR) criteria (12), and/or a positive biopsy of the temporal artery, and/or the presence of large-vessel vasculitis in any of the following imaging techniques: ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) scan, magnetic resonance imaging angiography (MRI-A), computed tomography angiography (CT-A), or helical CT scan.

The treatment of GCA was based on the classic pharmacological scheme, starting with high doses of GC. Conventional synthetic immunosuppressant and biologic drugs were used as GC-sparing agents, mainly in patients with a relapsing disease or in those with GC-side effects.

As indicated by the Spanish National Guidelines for the administration of biologic disease-modifying anti-rheumatic drugs (bDMARDs) in rheumatologic diseases, the presence of infectious diseases, as well as malignancies, were ruled out before starting BT. A tuberculin skin testing (PPD) and/or an interferon assay (QuantiFERON), and chest radiography, were performed to exclude latent tuberculosis. In positive cases, prophylaxis with isoniazid was initiated at least 4 weeks before biological drug onset and was maintained for 9 months, according to the national guidelines (13-20).

TCZ was prescribed at standard intravenous (IV) dose (8 mg/kg/4 weeks) or subcutaneously (SC) (162 mg/week). In many cases, TCZ was prescribed off-labeling since it was indicated before its approval by the EMA for GCA

treatment. Therefore, written informed consent was obtained in all those cases. The study protocol was approved by the Clinical Research Ethics Committee (protocol no.: 2018.080).

Clinical definitions and laboratory data

Definitions of complete and partial remission and relapse have been previously described (17). To sum up, serum C-reactive protein (CRP) was considered to be increased when higher than 0.5 mg/dL. Erythrocyte sedimentation rate (ESR) greater than 20 mm/h in men or 25 mm/h in women was considered abnormal. Anaemia was defined when haemoglobin level was ≤11 g/dL.

Briefly, remission was defined as the absence of symptoms and normalisation of the acute phase reactants (CRP and ESR). Prolonged remission was considered if the patients persisted asymptomatic with normal acute phase reactant for at least 6 consecutive months. Relapse was defined as the recurrence of signs or symptoms of GCA along with an increase of ESR >20 mm/h in men or >25 mm/h in women and/or serum CRP >0.5 mg/dL at any time of the GCA outcome.

Concerning safety, a serious adverse event (SAE) was considered when a life-threatening event (fatal or requiring hospitalisation) occurred, intravenous antibiotics were required, or the process led to persistent or significant disability.

Outcome variables and data collection

The leading outcome variables were effectiveness and safety. The main effectiveness end-points were: a) prolonged remission and b) number of relapses. Other outcomes were clinical remission and normalisation of the laboratory acute-phase reactants, GC-sparing effect, and cost per year of treatment. To determine safety, the development of SAEs was evaluated at every visit.

These outcome variables were documented in each centre, according to a follow-up protocol agreed upon beforehand to the recruitment of patients. Information was stored in a computerised database, and to minimise entry mistakes, all data were double-checked.

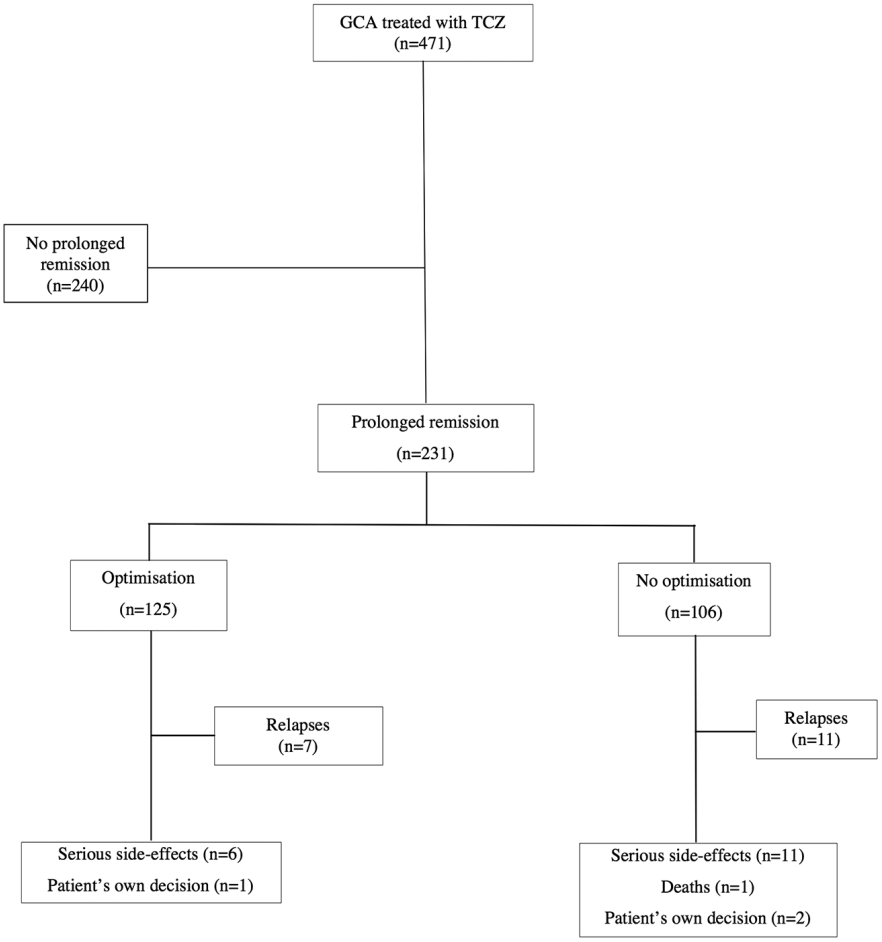

Fig 1. Flow chart of 471 patients with giant cell arteritis treated with tocilizumab.

Study of subgroups and statistical analysis

Of the 471 patients, we assessed those in which prolonged remission was achieved (n=231) (49%) (Fig. 1). At this moment, TCZ was maintained at standard dose or optimised. Optimisation was based on a shared decision between the patient and the physician. Optimisation was done by progressively reducing the TCZ dose and/or by increasing the TCZ dosing interval. Afterwards, we compared patients in whom TCZ was optimised (TCZ_{OPT} group) with those in which TCZ was maintained at the same doses and time intervals ($TCZ_{NON\text{-}OPT}$ group).

Results were expressed as mean ± standard deviation (SD) or median and interquartile range [IQR] [25^{th}, 75^{th}] as appropriate. Continuous variables were compared with the two-tailed Student's t-test or the Mann-Whitney U-test. The chi-square test or Fisher exact test were used to compare dichotomous variables and the Wilcoxon signed-rank test was used to compare continuous variables at different time points. Analyses were performed by using IBM SPSS Statistics, v. 28.0. Armonk, NY: IBM Corp.

Results

Main general features at TCZ onset

Two hundred and thirty-one (49%) of the 471 GCA patients achieved prolonged remission. Treatment optimisation was carried out in 125 of those who achieved prolonged remission, while 106 patients continued with the standard dose of TCZ. The baseline features of both groups at TCZ onset are summarised in Table I. There were no significant differences in demographic, clinical, and laboratory characteristics between both groups (Table I). However, the median prednisone dose was higher in the $TCZ_{NON\text{-}OPT}$ group (20 [10-45] *vs*. 15 [7.5-30] mg/day; p=0.017). Before TCZ onset, all patients had received oral GC and 54 (23.4%) were

treated with methylprednisolone (MP) boluses. One hundred and thirty-one (56.8%) patients were also treated with conventional immunosuppressive (IS) drugs: methotrexate (MTX) (n=121), azathioprine (AZA) (n=5), sulfasalazine (SSZ) (n=2), leflunomide (LFN) (n=1), mycophenolate (MMF) (n=1), cyclophosphamide (CYC) (n=1) and hydroxychloroquine (HCQ) (n=1).

The most frequent route of TCZ administration in both groups was intravenous (IV) (Table I). The initial dose was either 8 mg/kg/4 weeks IV or 162 mg/week subcutaneously (SC).

The first TCZ optimisation was performed after a median follow-up of 12 [6-17] months. Of the 125 patients in the TCZ_{OPT} group, 87 (69.6%) were on TCZ monotherapy and 38 (30.4%) were treated with a combination of TCZ and conventional IS drugs. No statistical differences with the $TCZ_{NON-OPT}$ group were found (Table I).

Follow-up and outcome variables

IV TCZ was optimised from 8 to 4 mg/kg/4 weeks in 26 of 59 (44%) patients and from 162 mg/SC/week to 162 mg/SC/every other week (eow) in 43 of 66 (65%) cases. Data of the optimised doses are shown in Supplementary Table S1.

After a median follow-up of 24 [19-24] (TCZ_{OPT} group) and 20 [14-24] months ($TCZ_{NON-OPT}$ group), prolonged remission was observed in 78.2% and 84.2%, respectively (p=0.296) (Table II).

In 23 (18.4%) of the 125 patients from the TCZ_{OPT} group, and after a progressive optimisation of TCZ, it was possible to withdraw the BT after a maintained remission of 23.5 [15-33] months. By contrast, in the $TCZ_{NON-OPT}$ group, TCZ was withdrawn in 14 of 106 patients (13.2%) after a median of 12 [6-17.5] months of prolonged remission.

Seven (5.6%) of the 125 optimised cases had a relapse and it occurred after 6 months of optimisation. Of the 7 patients with relapse, 4 received TCZ SC and 3 IV. In all of them, the relapse was treated by increasing the TCZ dose up to the pre-optimisation value. Relapses were not severe, 4 patients presented polymyalgia symptoms, 2 constitutional symptoms and one started with jaw claudication.

Table I. Main general features at TCZ onset of 231 GCA patients with prolonged remission.

	Optimised TCZ group (n=125)	Non-optimised TCZ group (n=106)	*p*
General features			
Age, years, mean± SD	72.7 ± 8.6	74 ± 8.7	0.197
Sex, female/male n (% female)	91/34 (72.8)	74/32 (69.8)	0.616
Time from GCA diagnosis to TCZ onset (months), median [IQR]	8 [2-21.5]	5 [2-21]	0.384
Previous treatment to TCZ onset, n (%)			
IV boluses MP	31 (24.8)	23 (21.7)	0.579
Methotrexate	73 (58.4)	48 (45.3)	0.047
Azathioprine	4 (3.2)	1 (0.9)	0.240
Sulfasalazine	2 (1.6)	-	0.295
Leflunomide	-	1 (0.9)	0.276
Mycophenolate	1 (0.8)	-	0.356
Cyclophosphamide	1 (0.8)	-	0.356
Hydroxycloroquine	1 (0.8)	-	0.356
Systemic manifestations, n (%)			
Fever	14 (11.2)	15 (14.2)	0.500
Constitutional symptoms	54 (43.2)	39 (36.8)	0.322
PMR	75 (60)	69 (65.1)	0.426
Ischaemic manifestations, n (%)			
Visual involvement	14 (11.2)	16 (15.1)	0.380
Headache	66 (52.8)	62 (58.5)	0.386
Jaw claudication	24 (19.2)	25 (23.6)	0.417
Aortitis (large-vessel involvement), n (%)	65 (52)	42 (39.6)	0.060
Laboratory findings			
ESR, mm/1st hour, median [IQR]	31 [15-59]	27 [11-52.5]	0.406
CRP, mg/dL median [IQR]	1.4 [0.5-2.8]	1.1 [0.4-3]	0.413
Haemoglobin, g/dL, median [IQR]	12.7 [11.6-13.7]	12.9 [12-14.2]	0.551
Glucocorticoids			
Prednisone dose, mg/d median [IQR]	15 [7.5-30]	20 [10-45]	0.017
Route of TCZ administration			
IV/SC, n (% IV)	72/53 (57.6)	64/42 (60.4)	0.669
Therapy			
Monotherapy/Combined treatment*, (% monotherapy)	87/38 (69.6)	81/25 (76.4)	0.246
Combined therapy, n (%)*			
Methotrexate	33 (26.4)	24 (22.6)	0.601
Azathioprine	5 (4)	-	0.037
Leflunomide	-	1 (0.9)	0.276

*Combined with conventional synthetic immunosuppressant agents.
CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; GCA: giant cell arteritis; IQR: interquartile range; IV: intravenous; PMR: polymyalgia rheumatica; SC: subcutaneous; SD: standard deviation; TCZ: tocilizumab.

In the $TCZ_{NON-OPT}$ group, a greater frequency of relapses (11 of 106 patients, 10.4%) was observed (*p*=0.17 between groups); 4 relapses occurred within the first 6 months after TCZ discontinuation. In this group, 6 patients were under IV treatment and 5 SC. Most relapsing patients presented systemic manifestations (4 polymyalgia symptoms and 4 constitutional symptoms), although there were also patients with ischaemic symptoms (2 headache and one jaw claudication). In addition, no difference was found between the prednisone dose of patients who suffered relapses and those who did not, in optimised and non optimised patients.

In both groups the median exposure time to prednisone was similar 12 [6-18] months. The median prednisone dose at first TCZ optimisation was 2.5 [0-5] mg/day. Interestingly, the GC-sparing effect achieved after TCZ onset was maintained once TCZ optimisation was performed (Fig. 2).

In the TCZ_{OPT} group, 29 patients (12.9 per 100 patients-year) reported SAEs compared to 26 patients (15.3 per 100 patients-year in the $TCZ_{NON-OPT}$ group (*p*=0.813). Serious infections occur in

15 patients (6.6 per 100 patients-year) in the TCZ_{OPT} group, and 22 in the $TCZ_{NON-OPT}$ group (12.9 per 100 patients-year) (p=0.009). (Table II).

Moreover, the mean cost of TCZ treatment was much lower in the TCZ_{OPT} group than in the $TCZ_{NON-OPT}$ group, being 7,621.9 €/patient/year *versus* 11,726 €/patient/year for the IV route, respectively. The correspondent figures for the SC administration were 6,107.5 *versus* 11,726 €/patients/year (Table II).

Table II. Follow-up of patients with refractory giant cell arteritis under TCZ treatment once prolonged remission was achieved.

	Optimised TCZ Group (n=125)	Non-optimised TCZ Group (n=106)	*p*
Follow-up on TCZ therapy (months), median [IQR]	24 [19-24]	20 [14-24]	0.001
Prolonged remission at the end of follow-up, n (%)	68/87 (78.2)	80/95 (84.2)	0.296
Patients with relapses, n (%)	7 (5.6)	11 (10.4)	0.177
Side effects, n (100 patients-year)			
Serious side-effects	29 (12.9)	26 (15.3)	0.813
Severe infections	15 (6.6)	22 (12.9)	0.009

IQR: interquartile range; TCZ: tocilizumab.

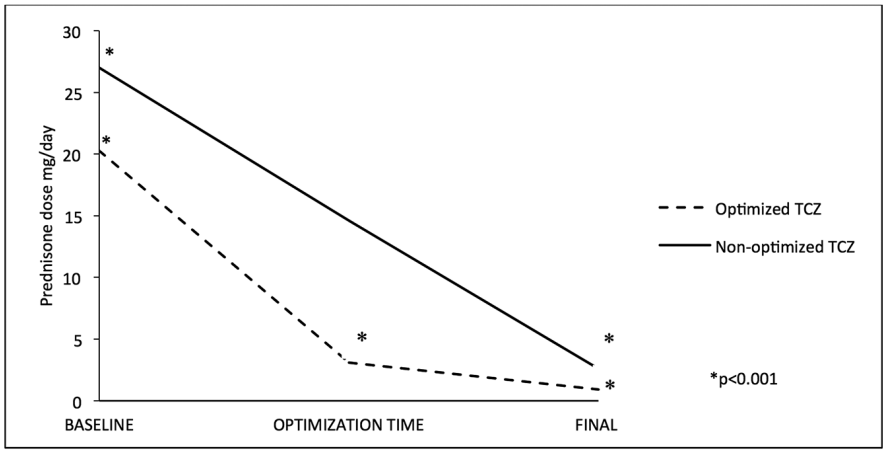

Fig. 2. Glucocorticoid-sparing effect following tocilizumab (TCZ) administration regardless of further optimisation.
*p-values for panels A and B show the differences between baseline findings and those observed at each period in every group, including the time of optimisation in the "optimised group". The assessment was performed in optimised and non-optimised patients.

Discussion

We provide data on TCZ optimisation in GCA patients that had reached prolonged remission. Patients in both groups (TCZ_{OPT} and $TCZ_{NON-OPT}$) presented similar demographic, clinical, and laboratory features at TCZ onset. After a progressive optimisation of BT, patients in the TCZ_{OPT} group maintained prolonged remission. As well, the frequency of relapses and serious adverse events was similar to the $TCZ_{NON-OPT}$ group. Interestingly, at the end of follow-up, serious infections and GC dose were significantly lower in the TCZ_{OPT} group. Also, as expected, the cost of TCZ optimisation was lower than non-optimised TCZ therapy.

Relapses are common in GCA. As pointed out in different series, up to half of the patients treated with GC in monotherapy have at least one flare occurring more frequently when the prednisone dose is lower than 10 mg daily or after the discontinuation of therapy. (3,6) As it is known, GC represent the main treatment of GCA, but the adverse events in elderly patients are frequent. Infections are the most common adverse event, as described by Tedeschi *et al*., serious infections are more frequent in the first year of diagnosis related with a higher mean daily glucocorticoid dose, another independent risk factor was older age (21). For this reason, several drugs are being studied for the treatment of GCA, but, to date, only TCZ has been approved for this condition (22). Even though TCZ has been shown to be effective in the clinical control of GCA, it remains to be unknown if TCZ leads to a complete resolution of vascular inflammation in imaging techniques. In this line, Prieto-Peña *et al*. reported a discordance between clinical and imaging activity assessment by PET/CT scan in patients with LVV/GCA undergoing TCZ therapy (23). Interestingly, it is unclear whether ongoing FDG vascular uptake is a risk for clinical relapse (24, 25).

TCZ is a humanised monoclonal antibody targeted against the IL-6 receptor that may be useful in several inflammatory/autoimmune diseases (11, 18-20), although the duration of treatment is not always well established.

In GCA, there is a general agreement on the initial and standard maintenance dose, but data on the duration of TCZ therapy are not well established. After one year of therapy and, once prolonged remission is achieved, there are three different scenarios; cessation, optimisation, or maintenance of TCZ at the same dose (Fig. 3).

In the extension phase of the GiACTA trial, when TCZ was discontinued, only 42% of patients who were in remission at week 52, were able to maintain clinical remission during the subsequent 2 years of follow-up. Therefore, abrupt discontinuation of this BT led to relapses in many patients, and therefore, optimisation of the treatment could be an appropriate alternative to avoid flares (10).

Similar studies on the optimisation of BT in other inflammatory diseases have shown good results (26-27, 31-37). In RA patients, TCZ optimisation demonstrated that efficacy is maintained, and the safety profile is adequate (38). In patients with refractory uveitis secondary to Behçet's disease, optimisation of anti-TNF-α agents was found to be also effective, safer, and more cost-effective than the standard regimen (13, 14).

In this study, we present the largest real-life multicentre series of GCA pa-

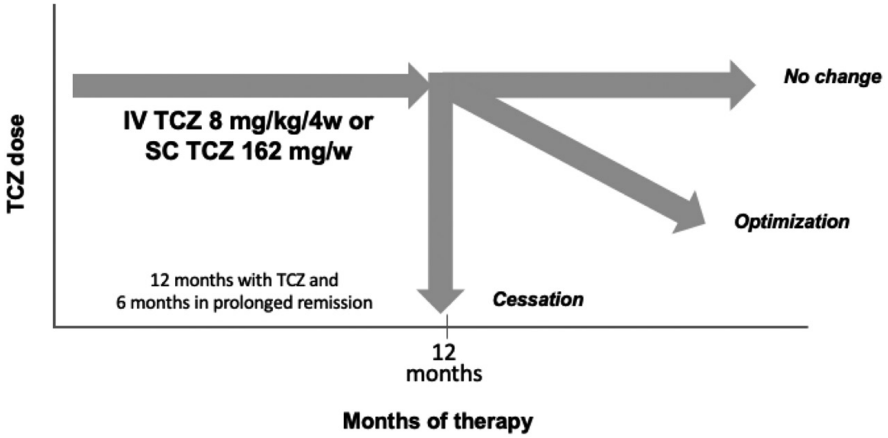

Fig. 3. Algorithm for TCZ therapy once prolonged remission is achieved: cessation optimisation, or maintaining the same dose.

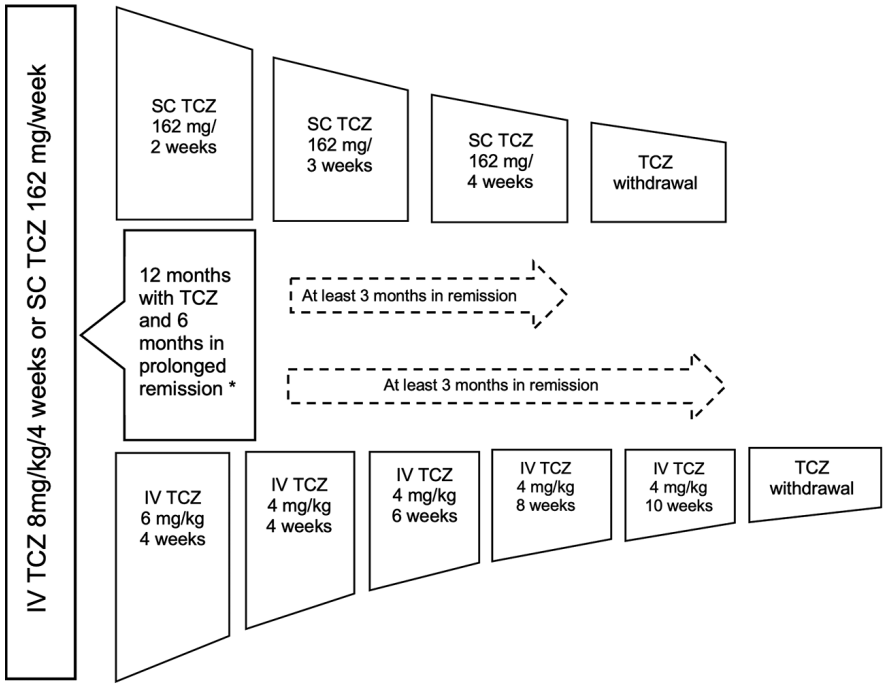

Fig. 4. Algorithm proposal for tocilizumab (TCZ) optimisation dose up to withdrawal by: A) prolonging the SC dosing interval (upper panel): B) decreasing doses and extending the IV dosing interval progressively (lower panel).
*In patients that had a PET/CT at GCA diagnosis or at TCZ onset, it could be considered to carry out a control PET/CT prior to TCZ optimisation.

tients on TCZ. When comparing the results of clinical trials with real-life settings, we realised that the characteristics of patients included in both studies are not similar. Besides, the frequency of serious infections in clinical practice is higher than the reported in the GiACTA trial, and it was related to a greater prednisone dose at TCZ onset and in the following three months of treatment (39). We also observed that TCZ had the same effectiveness when administered IV or SC (11).

In our series, when comparing general features of both groups, we realised that patients of TCZ_{OPT} group had a longer disease duration, received more conventional treatment and presented more large-vessel involvement, however, none of these data were statistically significant. Both groups, optimised and non-optimised patients, presented a maintained and similar improvement. Thus, 78.2% of patients presented a prolonged remission after TCZ optimisation. Moreover, only 5.6% of them relapsed after optimisation. Noteworthy, these patients had an adequate response after increasing TCZ up to the pre-optimisation dose. Interestingly, the GC-sparing effect achieved after TCZ onset was maintained once TCZ optimisation was carried out (Fig. 2). Another remarkable point is the lower incidence of serious infections once TCZ was optimised, 15 patients (6.6 per 100 patients-year) in the TCZ_{OPT} group, *vs*. 22 in the $TCZ_{NON\text{-}OPT}$ group.

The cost of standard per-protocol use of TCZ in Spain, for a person with a mean weight of 70 kg, is around 11,700 € for IV or SC administration. Regarding cost-effectiveness, optimisation after remission yielded a significant reduction of the mean cost of TCZ per patient-year, achieving an annual cost reduction of 35% for IV TCZ and 48% for SC TCZ.

After abrupt discontinuation of TCZ in patients with GCA in clinical remission, only 42% of them maintained this improvement (10). By contrast, in our series with a progressive optimisation, 78% of patients were in clinical remission after 2 years of follow-up.

Therefore, optimisation of the BT is an important option to decrease AEs frequency and reduce costs, maintaining the effectiveness of therapy. TCZ optimisation must be performed slowly by progressive increase of dosing interval and/or reduction of the BT dose (40).

Based on our experience, we propose a protocol for the optimisation of TCZ treatment in patients with GCA who achieve prolonged remission. In this regard, after 12 months of TCZ treatment and once prolonged remission was reached and maintained for at least 6 months, we recommend increasing slowly and progressively the dosing intervals of the SC or IV dose, always with regular monitoring of clinical and laboratory parameters (Fig. 4). Once the dosing interval has been increased up to every 12 weeks IV or every month SC, and prolonged remission is maintained, we recommend the discontinuation of treatment but keeping close monitoring. If relapse occurs, the previous TCZ dose should be restarted (Fig. 4).

Our study has several limitations due to its observational nature. Because

of that, further randomised controlled trials comparing both schedules are required. Nonetheless, it is difficult nowadays to carry out such a clinical trial. Therefore, future information will be probably obtained from observational multicentre studies, such as ours.

Conclusions

In GCA patients, TCZ optimisation may be done once prolonged remission is achieved by reducing the dose or increasing the dosing interval. This seems to be an effective, safe, and cost-effective therapeutic option.

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Competing interests

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